REMARKS

Telephone Interview

Applicants would like to express their appreciation for the courtesy extended by the Examiner to Applicants' agent, Angela Dallas Sebor, in the telephone interview on November 17, 2004. During the interview, Dr. Sebor discussed the remaining rejection under 35 U.S.C. § 103, and particularly presented additional arguments regarding the cited combination and specifically, the Lobb et al., Wigzell et al., Schramm et al., and Krause et al. references. The Examiner indicated that Dr. Sebor should reiterate these comments in a written response for further consideration by the Examiner. The Examiner indicated that it appeared that there were new issues to consider particularly with regard to Lobb et al. based on Dr. Sebor's comments.

Rejection of Claims 1, 2 and 9-35 Under 35 U.S.C. § 103:

The Examiner has maintained the rejection of Claims 1, 2 and 9-35 under 35 U.S.C. § 103, contending that these claims are not patentable over Lobb et al. (U.S. Patent No. 5,871,734) as evidenced by Arrhenius et al. (U.S. Patent No. 5,869,448), in view of Schramm et al., Wigzell et al. (U.S. Patent No. 5,958,410), and Krause et al. (USPAP 2002/0037286).

Applicants traverse the Examiner's rejection under 35 U.S.C. § 103. Applicants note that for the Examiner to establish a *prima facie* case of obviousness, the combination of references must: (1) teach each and every element of the claimed invention; (2) provide the requisite motivation to combine the references to arrive at the claimed invention; and (3) provide a reasonable expectation of success to arrive at the claimed invention. As discussed with the Examiner in the November 17 telephone interview, Applicants submit that the combination of references particularly fail to provide the requisite motivation to combine the references to arrive at the claimed invention and further, fail to provide a reasonable expectation of success to arrive at the claimed invention. Moreover, Applicants submit that the combination of references fails to teach or suggest an *aerosolized antibody* having one of the particularly recited receptor specificities, *wherein the binding of the antibody to the receptor causes the depletion or inactivation of the T cell.*

Specifically, the Examiner contends that Lobb et al. teach the use of aerosolized anti-VLA4 to treat asthma, and that, as evidenced by Arrhenius et al., VLA4 is a receptor on T cells. The

Examiner acknowledges that Lobb et al. do not teach the use of anti-αβ T cell receptor antibodies, but submits that Schramm et al. teach the use of intravenously administered anti-αβ TcR to treat asthma. The Examiner asserts that it would have been prima facie obvious to have created the claimed invention because "Lobb et al. teach aerosol administration of an antibody which binds T cells to treat asthma and Schramm et al. teach that a different antibody which binds T cells (antiTCR αβ) can be used to treat asthma." The Examiner contends that in addition, Krause et al. teach that antibodies that inhibit T cell activation are preferably administered via aerosol and that Wigzell et al. teach that pathologic T cells found in the lungs can be treated by intrapulmonary administration of anti-TCR antibodies. Motivation is alleged based on the teachings of Krause et al. and Wigzell et al. and also because Lobb et al. allegedly teach that anti-T cell antibody can be administered in a variety of routes including aerosol. With regard to Applicants' arguments regarding the cellular specificity of VLA4, given that the anti-VLA4 antibody binds T cells and given that the antibody of Schramm et al binds T cells, the Examiner submits that it is reasonable to conclude that the antibody of Schramm et al. could be used in the method of Lobb et al.

However, in contrast to the Examiner's conclusions regarding Lobb et al., Applicants submit that the anti-VLA4 antibody of Lobb et al. is shown by Lobb et al. to have *no effect* on the T cell count in the animals to which the antibody is administered, and Lobb et al. in fact teach that the asthma inhibitory effects are instead associated with effects on neutrophils and eosinophils. Specifically, as previously argued by Applicants, and as supported by Arrhenius et al. (col. 1, lines 54-65), anti-VLA4 binds to *a variety of cell types* in addition to T cells. Furthermore, Lobb et al. provide a clear teaching that anti-VLA4 administration in a model of asthma causes a significant inhibition of the recruitment of neutrophils and eosinophils to the lung (column 3, lines 4-7 and column 12, lines 10-21), and further provide data showing that anti-VLA4 treatment has no effect on number of lymphocytes (e.g., T cells) in the lung. Moreover, as discussed with the Examiner in the November 17 interview, the data of Lobb et al. show that not only did anti-VLA4 *not have an effect* on the T cell numbers or recruitment, as clearly shown by Fig. 4B of Lobb et al., it appears as though anti-VLA4 may have actually *increased* the lymphocytes in the lungs of the animal. Therefore, Lobb et al. do not teach or suggest the use of an aerosolized antibody that binds to a receptor on T cells to treat asthma, wherein the binding of the antibodies to the receptor causes the

depletion or inactivation of the T cells. One can not conclude that anti-VLA4 had any effect on T cells or that the reduction in airway hyperresponsiveness was due to any effect on T cells from the teachings of Lobb et al. Applicants have previously argued that Lobb et al. teach that their method operates by inhibiting the recruitment of primarily eosinophils and neutrophils to lung tissue (see Response filed May 13, 2003), and this data in Lobb et al. (see Figs. 4A-4D), as well as the statements by Lobb et al. referenced above are noted in further support of this conclusion.

Therefore, Lobb et al. do not appear to teach an aerosolized antibody that binds to a T cell receptor and causes the depletion or inactivation of the T cell, nor the modulation of T cells to treat asthma, nor would the teachings of Lobb et al. motivate one of skill in the art to look at the modulation of T cells to treat asthma or airway hyperresponsiveness. At best, the teachings of Lobb et al. would suggest that one might look at methods of targeting *eosinophils or neutrophils* to treat asthma, and could further suggest that modulation of T cells is not necessary, or is not effective using an anti-VLA4 antibody. This is a *teaching away* from the present invention. Applicants' position and the teachings of Lobb et al. directly rebut the Examiner's position that, given that the anti-VLA4 antibody binds T cells and given that the antibody of Schramm et al binds T cells, it is reasonable to conclude that the antibody of Schramm et al. could be used in the method of Lobb et al. This is clearly not a reasonable conclusion based on the Lobb et al. disclosure.

The Examiner argues that the combination of Lobb et al. with Schramm et al., and further with Wigzell et al. and Krause et al., will motivate one of skill in the art to substitute the antibody of Schramm et al. into the method of Lobb et al., and that one of skill in the art would expect success because of the successful use of aerosolized antibody by Lobb et al. and the further teachings of aerosol administration by Wigzell et al. and Krause et al. Applicants disagree. First, it should now be clear that Lobb et al. do not teach or suggest the method of the present invention, and in fact, provide absolutely no motivation or expectation of success at targeting a T cell to treat asthma. Therefore, any suggestion or motivation to make the combination of references, to remedy the deficiencies of Lobb et al., or to teach or suggest the invention at all must come from the other references in the combination. The other references do not meet this requirement.

Schramm et al. is a research study showing that *complete, systemic depletion* of an entire T cell subset ($\alpha\beta$ or $\gamma\delta$) from an animal, either by genetic manipulation or by intravenous antibody

administration, prevents the development of airway inflammation and bronchial hyperactivity in mice. The study is primarily directed to determining the role of γδ T cells in asthma, and also to dissect the roles of the two T cell subsets. Schramm et al. do not teach or suggest *the therapeutic use* of any antibodies for the treatment of asthma. Indeed, complete, systemic depletion of T cells would *never* be viewed by one of skill in the art as a therapeutic approach to treatment of a disease, including airway inflammation and/or hyperresponsiveness, because of course complete, systemic depletion of a major arm of the immune system as a therapy would have undesirable consequences for the animal. Moreover, Schramm et al. do not teach or suggest the use of aerosolized antibodies or the administration of antibodies to the lung of an animal. One simply can not learn from the teachings of Schramm et al. that one could or should therapeutically deplete or inactivate the pulmonary T cells in an animal to treat airway hyperresponsiveness in the animal, and moreover, one can not learn from the teachings of Schramm et al. that one can deplete pulmonary T cells and treat airway hyperresponsiveness without substantially effecting peripheral T cells in the animal. Schramm et al. is not concerned with such topics and so there is no suggestion, motivation or expectation of success provided by Schramm et al. to make or use the present invention, even when combined with the other references. There is absolutely no motivation or suggestion in any of the references in the cited combination to move the antibody of Schramm et al. into *any* therapeutic method, let alone the method of Lobb et al., which only suggests targeting eosinophils or neutrophils via blocking of an adhesion molecule.

Wigzell et al. and Krause, even when combined with Lobb et al. and Schramm et al., do not remedy the above-described deficiencies. Wigzell et al. characterizes T cells from the lungs of patients with sarcoidosis and identifies a particular subset of T cell receptors that appear to be increased in patients with sarcoidosis. Wigzell et al. suggest making an antibody to this T cell receptor and include intrapulmonary administration in a listing of a variety of administration routes. Wigzell et al. teach treating sarcoidosis, which is not related to asthma or airway hyperresponsiveness and thus, provides no suggestion or no motivation to develop a method to treat asthma. Therefore, there is no motivation to combine this reference with either of Lobb et al. or Schramm et al. The antibody of Wigzell et al. is also a <u>blocking</u> antibody (see col. 9, lines 40-43; col. 12, lines 57-62;), which is not an antibody that depletes or inactivates T cells, regardless of how

it is administered, and thus does not meet the present claim limitations. Finally, Wigzell et al. provide no demonstration of the actual administration *in vivo* of the antibody in any form, including by aerosol, and so regardless of whether or not Wigzell et al. teach through a list of various possible routes that one route of administration is intrapulmonary, one of skill in the art has absolutely no expectation that aerosol administration of the Wigzell et al. antibody to treat *any* disease would be successful. Therefore, this reference fails to remedy the deficiencies of the combination of Lobb et al. and Schramm et al.

Similarly, Krause et al. teaches the identification of a protein associated with actin cytoskeletal reorganization called "Fyb/SLAP", which, as with the VLA4 of Lobb et al., is <u>not</u> T cell-specific (the protein is expressed also by macrophages, platelets, and perhaps other hematopoietic cells). Krause et al. teach that one may produce an antibody that selectively binds to Fyb/SLAP and administer the antibody to an animal to regulate cytoskeletal reorganization in the animal. In teaching administration of the therapeutics of their invention, Krause teach a variety of routes, including a preference for pulmonary aerosol for antibodies. The method of regulation of cytoskeletal reorganization is not related to asthma or airway hyperresponsiveness, and thus, provides no suggestion or no motivation to develop a method to treat asthma. Therefore, there is no motivation to combine this reference with either of Lobb et al. or Schramm et al. The antibody of Krause et al. is not T cell specific and is a blocking antibody (see section 0008, 0104, 0105), which is not an antibody that binds to any of the recited T cell receptors and is not an antibody that depletes or inactivates T cells, and therefore does not meet the present claim limitations. Finally, Krause et al. provide no demonstration of the actual administration *in vivo* of any antibody in any form, including by aerosol, and so regardless of whether or not Krause et al. teach that one route of administration is intrapulmonary, one of skill in the art has absolutely no expectation that aerosol administration of the Krause et al. antibody to treat *any* disease would be successful. Therefore, this reference fails to remedy the deficiencies of the combination of Lobb et al. and Schramm et al.

In summary, in view of the discussion above, the combination of references fails to teach or suggest the use of aerosolized antibody that binds to and depletes or inactivates the recited T cells receptors, whereby aerosolized administration of said antibodies reduces airway hyperresponsiveness in a mammal. Moreover, the combination fails to provide any motivation to make the combination

as the Examiner has done, or to motivate one to make and use the present invention. Finally, the combination does not provide any expectation of success at making and using the present invention. Therefore, the Examiner has not established a *prima facie* case of obviousness in view of the combination of references.

The Examiner also asserts that Fahy et al. is not germane to the present argument because the most likely explanation for the results of Fahy et al. is that the soluble IgE was sequestered in an "IgE sink" in the vascular space, whereas Applicants' antibody does not bind to a soluble antigen. Moreover, the Examiner contends that the teachings of Lobb et al., Krause et al. and Wigzell et al. rebut the argument that aerosolized antibodies are not always effective.

Applicants disagree. The point of referencing Fahy et al. was in response to the Examiner's combination of Lobb et al. and Schramm et al. based in part on the argument that it would be expected that the antibody of Schramm et al. would treat asthma even if administered by aerosol. Fahy et al. is clearly a good example that provision of a therapeutic effect by administration of antibodies systemically does not necessarily make it obvious that the same effect will be provided when the same antibody is administered by aerosol. Since Fahy et al. only hypothesized as to the reasons for the failure of aerosol delivery, one can not dismiss the results merely on the basis that the targeted IgE is a soluble protein. Furthermore, the teachings of Wigzell et al. and Krause et al. do not at all contradict the findings of Fahy et al., as neither of Wigzell et al. or Krause et al. had any demonstration of the administration of an antibody in aerosol form.

Finally, regarding the recited advantages of the claimed invention, the Examiner again refers to Krause et al. and Wigzell et al., and further states that comments regarding γδ T cells are not relevant because they relate to a non-elected species.

In response, Applicants again assert that, in addition to the failure of the combination of references to establish a *prima facie* case of obviousness as discussed above, the present invention provides the following advantages as compared to the art at the time of the invention. Moreover, as stated above, Wigzell et al. and Krause et al. do not provide an actual administration *in vivo* of any antibody in any form, and so regardless of whether or not these patents mention that one can administer an antibody by intrapulmonary routes, one of skill in the art has absolutely no expectation that aerosol administration of any dose of their antibody to treat *any* disease would be successful.

First, the claimed method targets pulmonary T cell populations in the absence of any substantial effect on peripheral T cells, which is a large advantage over any methods which target T cell responses systemically, because the systemic immune response remains intact. As discussed in the last response, Applicants have demonstrated this effect through working examples.

Second, in contrast to the evidence and assertions generally in the art that antibodies delivered by aerosol must be administered in high doses to overcome the effects of expected low potency and to successfully reach the target airways, the present inventors have demonstrated that the claimed method of aerosol administration is highly effective at reducing airway hyperresponsiveness, and is effective at extremely *low* doses of antibody. Indeed, the method of the present invention achieves efficacy with antibody doses that are believed to be about *1000-fold* or more lower than systemic doses of antibody required to achieve the same effect. It is not believed to be necessary to import dose limitations into the present claims because the claimed method also operates at higher doses of antibody, and further because Applicants submit that the Examiner's *prima facie* case of obviousness fails regardless for the reasons set forth above, regardless of the dose of antibody administered. The advantages of the invention only further separate the claimed invention from the art. Again, as discussed in the last response, Applicants have demonstrated this effect through working examples.

Finally, with regard to the non-elected species of γδ T cells, selective targeting of γδ T cells for depletion has the advantage of not targeting cells that participate in the adaptive immune response (e.g., αβ T cells or B cells). Similarly, with regard to the elected species, selective targeting of αβ T cells for depletion has the advantage of not targeting the humoral immune response or cells that participate in the non-adaptive immune response (γδ T cells).

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 2 and 9-35 under 35 U.S.C. § 103.

Applicants have attempted to respond to the Examiner's rejections as set forth in the June 22 Office Action, and submit that the claims are in a condition for allowance. In the event that the Examiner has any remaining concerns regarding Applicants' position, he is encouraged to contact the below-named agent at (303) 863-9700 to expedite the allowance of this application.

Respectfully submitted,

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